EXPAREL®
(bupivacaine liposome injectable suspension)

Administration Technique Guide

Capturing Clinician Experience With EXPAREL

This educational technique guide represents the individual experience of Dr. Lawrence Biskin and is intended to demonstrate his methodology for using EXPAREL in a specific soft tissue surgery.* Pacira Pharmaceuticals recognizes that there are alternative methodologies for administering local anesthetics, as well as individual patient considerations, when selecting the dose for a specific procedure.

Please see Important Safety Information on reverse and refer to the accompanying full Prescribing Information before using EXPAREL for complete Dosage and Administration information.

CASE INFORMATION

Physician Name	Dr. Lawrence Biskin
Affiliation	UPMC Saint Margaret Memorial Hospital
Surgical Case Performed	Laparoscopic cholecystectomy
Inpatient or Outpatient Procedure	Outpatient

PATIENT CHARACTERISTICS

Gender	Female
Age	61 years
Patient History and Characteristics	Height: 5'3" Weight: 157 lbs

INFILTRATION TECHNIQUE

Incision Size	**3 trocar sites:** Two 5 mm incisions, one 3 mm incision **1 camera port:** One 10 mm umbilicus incision for camera insertion
Preoperative Analgesics Used	IV acetaminophen
Intraoperative Analgesics Used	None
Was EXPAREL Diluted? If so, to What Volume?	One 20 cc vial of EXPAREL (266 mg)
Depth and Volume of EXPAREL Infiltrated at Each Site	**5 mm incisions:** 5 cc EXPAREL is infiltrated subcutaneously and into the fascia in each incision **10 mm incision:** 10 cc EXPAREL is infiltrated into the fascia circumferentially around the umbilicus

FOLLOW-UP NOTES

Additional Postsurgical Medications Used/Prescribed	None prescribed; patient was instructed to take standard OTC analgesics as needed
Other Observations	Patient reported no incisional pain following the procedure and required no opioids for pain control. Some shoulder pain resulting from the insufflation was reported.

*The approval of EXPAREL was based on 2 pivotal clinical trials that demonstrated the safety and efficacy of the product injected into soft tissue surrounding the surgical site. In the pivotal soft tissue trial (an excisional hemorrhoidectomy), a dose of 266 mg of EXPAREL (one 20-mL vial) was diluted with 10 mL of preservative-free normal sterile saline for a total volume of 30 mL. The solution was infiltrated circumferentially in 6 aliquots around the anus. In the pivotal orthopedic trial (a bunionectomy), an undiluted dose of 106 mg of EXPAREL (8 mL) was administered into the wound.

Because local analgesics act at the site of administration, and pharmacokinetics are not predictive of efficacy, it is up to the individual prescriber to determine the relevance of the demonstration of efficacy and safety in these surgical models to their own surgical setting.

The dose of EXPAREL is based on the surgical site and the volume required to cover the area. The maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug).

EXPAREL is a liposomal formulation of bupivacaine indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia.

Important Safety Information:

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. EXPAREL has not been studied for use in patients younger than 18 years of age. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL. Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

PACIRA PHARMACEUTICALS, INC.

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Administration Technique Guide

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This educational technique guide represents the individual experience of Dr. Stephen M. Cohen, MD, FACS, FASCRS and is intended to demonstrate his methodology for using EXPAREL in a specific soft tissue surgery.* Pacira Pharmaceuticals recognizes that there are alternative methodologies for administering local anesthetics, as well as individual patient considerations, when selecting the dose for a specific procedure.

CASE INFORMATION

Physician Name	Stephen M. Cohen, MD, FACS, FASCRS
Affiliation	Atlanta Colon and Rectal Surgery, P.A.; Atlanta, GA
Surgical Case Performed	Open colectomy (ileocolic resection) with repair of the fistula
Inpatient or Outpatient Procedure	Inpatient

PATIENT CHARACTERISTICS

Gender	Male
Age	22 years of age
Patient History and Characteristics	• Long history of Crohn's Disease • Six-month history of weight loss, nausea, vomiting, diarrhea • Large segment of inflammation in his terminal ileum with a small bowel to colon fistula

PROCEDURAL DETAILS

Incision Size	8-cm vertical midline incision and ostomy
Preoperative Analgesics Used	IV acetaminophen 1000 mg 30 minutes prior to incision
Intraoperative Analgesics Used	None
Was EXPAREL Diluted? If so, to What Volume?	One 20 cc vial (266 mg) was diluted with 20 cc preservative-free normal sterile saline for a total volume of 40 cc

FOLLOW-UP NOTES

Other Observations	Patient required no PCA device or epidural for rescue medication and reported well-controlled pain the first night postsurgically

*The approval of EXPAREL was based on two pivotal clinical trials, excisional hemorrhoidectomy and bunionectomy, that demonstrated the safety and efficacy of the product. In the excisional hemorrhoidectomy trial, 266 mg of EXPAREL (one 20-mL vial) was diluted with 10 mL of preservative-free normal sterile saline. In the bunionectomy trial, an undiluted dose of 106 mg (8 mL) was used.

In the excisional hemorrhoidectomy trial, EXPAREL demonstrated postsurgical pain control with reduced opioid requirements for up to 72 hours. The median time to first opioid rescue was 14.3 hours for EXPAREL vs 1.2 hours for placebo. 28% of patients treated with EXPAREL received no postsurgical opioid rescue through 72 hours vs 10% of placebo-treated patients. The clinical benefit of the attendant decrease in opioid consumption was not demonstrated.

It is up to the individual prescriber to determine the relevance of the demonstration of efficacy and safety in these surgical models to their own surgical setting. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area. The maximum dosage of EXPAREL should not exceed 266 mg.

Please see Important Safety Information on reverse and refer to the accompanying full Prescribing Information before using EXPAREL for complete Dosage and Administration information.

INFILTRATION TECHNIQUE

- Approximately 5 cc of EXPAREL is infiltrated directly into the fascia and around the umbilicus along the length of the left side of the midline incision. (Figure 1)
- Approximately 15 cc of EXPAREL is slowly injected along the length of the incision starting at the superior position with the needle inserted under the skin several centimeters lateral to the left side of the incision. (Figure 2)
  - The goal of this technique is to achieve a field block that encompasses the area around the incision, including part of the ileostomy. (Figure 3)
- The final 20 cc of EXPAREL is infiltrated in the same fashion on the right side of the incision. (Figure 4)
- Once the patient has healed enough for ileostomy closure, 20 cc of undiluted EXPAREL (266 mg) will be injected circumferentially around the site, with 25% of EXPAREL injected into the fascia and the remainder infiltrated using a lateral needle in a fanning fashion to obtain a field block around the ostomy.

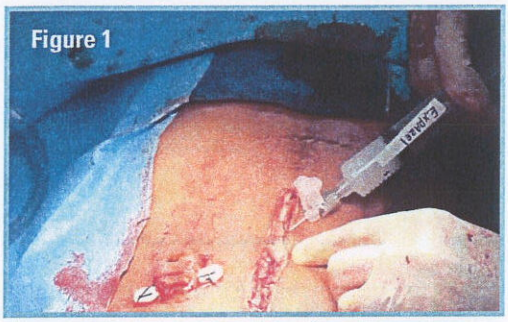
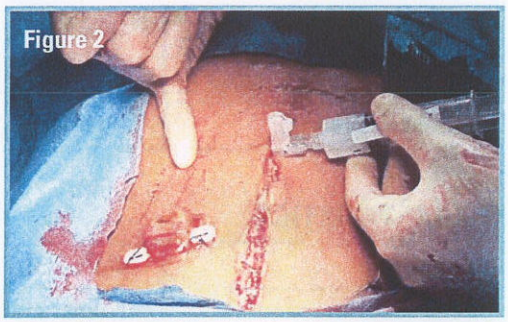


Figure 1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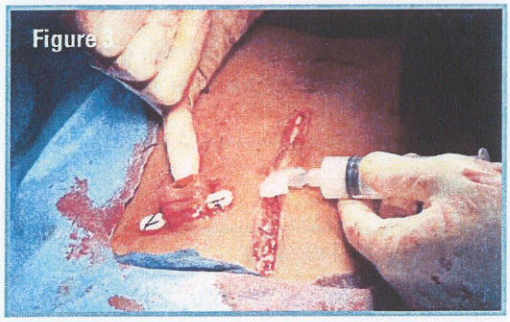
Figure 3

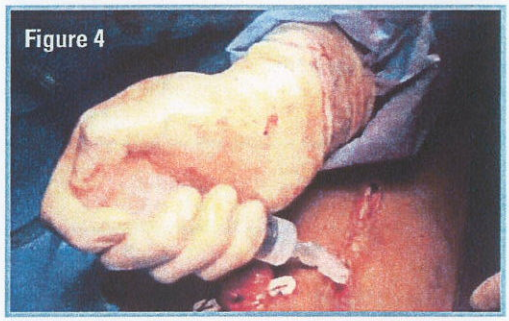
Figure 4

EXPAREL is a liposomal formulation of bupivacaine indicated for single-dose administration into the surgical site to produce postsurgical analgesia.

Important Safety Information:

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. EXPAREL has not been studied for use in patients younger than 18 years of age. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL. Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

Disclosures: Dr. Cohen is a paid speaker and consultant for Pacira.

Scan here to see a video of this infiltration.

PACIRA PHARMACEUTICALS, INC.

For the Management of Postsurgical Pain

EXPAREL® (bupivacaine liposome injectable suspension)

Patient-Focused Pain Control That Lasts For Up To 72 Hours

The only single-dose local analgesic to

- **Reduce or eliminate** opioids with pain control for up to 3 days
- **Without** the need for catheters or pumps

Pivotal studies have demonstrated the safety and efficacy of EXPAREL in patients undergoing bunionectomy and hemorrhoidectomy procedures.

The clinical benefit of the attendant decrease in opioid consumption was not demonstrated.

EXPAREL is a liposome formulation of bupivacaine indicated for administration into the surgical site to produce postsurgical analgesia.

Important Safety Information:

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. EXPAREL has not been studied for use in patients younger than 18 years of age. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL. Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

Reference: Gorfine SR, et al. *Dis Colon Rectum.* Dec 2011;54(12):1552-1559.

Please see brief summary of Prescribing Information on reverse side.

For more information, visit www.EXPAREL.com

EXPAREL®
(bupivacaine liposome injectable suspension)
PATIENT-FOCUSED PAIN CONTROL

EXPAREL

(bupivacaine liposome injectable suspension)

PATIENT-FOCUSED PAIN CONTROL

Brief Summary (For full Prescribing Information please see package insert)

INDICATIONS AND USAGE: EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

EXPAREL has not been studied for use in patients younger than 18 years of age.

CONTRAINDICATIONS: EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

WARNINGS AND PRECAUTIONS

Warnings and Precautions for Bupivacaine Containing Products: The safety and effectiveness of bupivacaine and other amide-containing products depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity *[See Overdosage (10)]*.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine and other amide-containing products. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Bupivacaine and other amide-containing products should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Injection of multiple doses of bupivacaine and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Central Nervous System Reactions: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesias, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure *[See Warnings and Precautions (5.1) and Overdosage (10)]*.

Allergic Reactions: Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis: Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of glenoid-humeral chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Warnings and Precautions Specific for EXPAREL: As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.

Caution should be taken to avoid accidental intravascular injection of EXPAREL.

Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL.

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration: epidural, intrathecal, regional nerve blocks, intravascular or intra-articular use.

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups: patients younger than 18 years old, pregnant patients, nursing patients.

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

ADVERSE REACTIONS: The most commonly encountered acute adverse experiences to bupivacaine and all amide-type local anesthetics that demand immediate counter-measures are related to the central nervous and cardiovascular systems.

High plasma concentrations of bupivacaine can occur from overdosage, unintended intravascular injection, or accumulation of bupivacaine in plasma secondary to decreased hepatic metabolic degredation of the drug or diminished plasma protein binding capacity due to acidosis, pathologically lowered plasma protein production, or competition with other drugs for protein binding sites. Although rare, some individuals have a lower tolerance to and are supersensitive to bupivacaine and other amide-type local anesthetics and may rapidly develop signs of toxicity at low doses [See **OVERDOSAGE**].

Adverse Reactions Reported in All Wound Infiltration Clinical Studies: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary retention, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions Reported in All Wound Infiltration Clinical Studies: In the EXPAREL wound infiltration studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were dizziness (6.2%), headache (3.6%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in Placebo-Controlled Wound Infiltration Clinical Studies: Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 8 mL EXPAREL 1.3% (106 mg) to placebo and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 1.

Table 1: Treatment-Emergent Adverse Reactions (TEAE) with an Incidence Greater than or Equal to 2% Placebo-Controlled Studies

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL 8 mL/1.3% (106 mg)	Placebo	EXPAREL 20 mL/1.3% (266 mg)	Placebo
System Organ Class Preferred Term	(N=97) n (%)	(N=96) n (%)	(N=95) n (%)	(N=94) n (%)
Any TEAE	63 (64.9)	59 (61.5)	16 (16.5)	17 (18.1)
Gastrointestinal Disorders	41 (42.3)	38 (39.6)	7 (7.4)	13 (13.8)
Nausea	36 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Constipation	2 (2.1)	1 (1.0)	2 (2.1)	2 (2.1)
Anal Hemorrhage	0 (0.0)	0 (0.0)	3 (3.2)	4 (4.3)
Painful Defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Rectal Discharge	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.2)
Nervous System Disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Pruritus Generalized	5 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)
Alanine Aminotransferase Increased	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Aspartate Aminotransferase Increased	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	0 (0.0)	0 (0.0)	3 (3.2)	3 (3.2)
General Disorders And Administration Site Conditions	4 (4.1)	0 (0.0)	1 (1.1)	1 (1.1)
Feeling Hot	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (2.1)	0 (0.0)	1 (1.1)	1 (1.1)
Infectious And Infestations	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Fungal Infection	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Swelling	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)

[a] Study 1: Bunionectomy [b] Study 2: Hemorrhoidectomy

At each level of summation (overall, system organ class, preferred term), patients are only counted once. Preferred terms are included where at least 2% of patients reported the event in any treatment group. TEAE = treatment-emergent adverse event.

DRUG INTERACTIONS: EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e., 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. EXPAREL must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles.

EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics.

EXPAREL may be locally administered after at least 20 minutes following local administration of lidocaine.

EXPAREL should not be admixed with other drugs prior to administration.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. EXPAREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Bupivacaine hydrochloride (HCl) produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of EXPAREL at term for analgesia.

Bupivacaine HCl was administered subcutaneously to rats and rabbits during the period of fetal organogenesis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity. Administration of bupivacaine HCl to rats during pregnancy and lactation resulted in decreased offspring survival.

Labor and Delivery: Bupivacaine hydrochloride is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Nursing Mothers: Bupivacaine has been reported to be excreted to some extent in human milk, suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer EXPAREL, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric Use: Of the total number of patients in the EXPAREL wound infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL.

Hepatic Impairment: Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Renal Impairment: Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection of EXPAREL.

OVERDOSAGE: Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution *[See **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**]*.

In the clinical study program, maximum plasma concentration (Cmax) values of approximately 34,000 ng/mL were reported and likely reflected inadvertent intravascular administration of EXPAREL or systemic absorption of EXPAREL at the surgical site. The plasma bupivacaine measurements did not discern between free and liposomal-bound bupivacaine making the clinical relevance of the reported values uncertain; however, no discernable adverse events or clinical sequelae were observed in these patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals of most local anesthetics, including bupivacaine, to evaluate the carcinogenic potential have not been conducted. Mutagenic potential and the effect on fertility have not been determined. There is no evidence from human data that bupivacaine may be carcinogenic or mutagenic or that it impairs fertility.

DOSAGE AND ADMINISTRATION: EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy[1]	106 mg	8 mL
Hemorrhoidectomy[2]	266 mg	20 mL

[1]Infiltrate 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

[2]Dilute 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, and divide the mixture into six 5 mL aliquots. Perform the anal block by visualizing the anal sphincter as a clock face and slowly infiltrate one aliquot to each of the even numbers.

Injection Instructions: EXPAREL should be injected slowly into soft tissues of the surgical site with frequent aspiration to check for blood and minimize the risk of intravascular injection. EXPAREL is intended for single-dose infiltration only. EXPAREL should be administered with a 25 gauge or larger bore needle, the maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug), do not administer EXPAREL if the product is discolored, do not administer EXPAREL if it is suspected that the vial has been frozen as reflected by the temperature indicator or exposed to high temperature (greater than 40°C or 104°F) for an extended period, EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection, vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial. Diluted suspensions of EXPAREL should be used within 4 hours of preparation in a syringe.

Administration Precautions: Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is not recommended:

Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine. When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

Non-Interchangeability with Other Formulations of Bupivacaine: Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

Dosing in Special Populations: EXPAREL has not been studied in patients younger than 18 years of age, pregnant patients or patients who are nursing.

PATIENT COUNSELING INFORMATION: Patients should be informed in advance that bupivacaine-containing products can cause temporary loss of sensation or motor activity in the area infiltrated. Physicians should discuss adverse reactions in the EXPAREL prescribing information with their patients.

Pacira Pharmaceuticals, Inc., San Diego, CA 92121 USA

Patent Numbers: 6,132,766 5,766,627 5,891,467

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For additional information call 1-855-RX-EXPAREL (1-855-793-9727)

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